In the Specification

Please replace paragraphs 6-9 with the following rewritten paragraphs.

[006] ~~Fig. 1~~ Figures 1A-1B: Protein domains analyzed for K8/K18 mutations and an example of the identification of a K8 mutation. (A) A central rod domain, consisting of α-helical subdomains, is flanked by non- α-helical head/tail domains. The head/tail domains are further subdivided into E, V and H regions. The subdomains of the rod are connected by nonhelical linker (L1, L1-2, L2) regions. The amino acid (aa) regions in black bars represent 5 domains that were examined for K8/K18 mutations. The remaining regions in gray bars contain 10 exonic K8/K18 domains that have been analyzed for mutations. (B) PCR products, from a control patient (with K8 WT) and a patient with K8 R340H, were analyzed by denaturing HPLC using a WAVE® System. The control (K8 WT) is characterized by one major peak, while the K8 R340H shows a different chromatogram due to resolution of the homoduplexes from the heteroduplexes, thereby suggesting the presence of a K8 mutation. Electropherograms from DNA sequencing confirm the presence of a K8 R340H heterozygous missense mutation (CGT→CAT).

[007] ~~Fig. 2~~ Figures 2A-2B: Protein expression of mutant K8 and K18 in explanted livers. (A): K8/K18 immunoprecipitates were obtained from 1% Empigen-solubilized normal liver or livers with keratin mutation. The immunoprecipitates were separated by isoelectic focusing followed by SDS-PAGE, then immunoblotting with anti-K8/K18 antibodies. Note that K8 and K18 in normal liver consist of two or three isoforms depending on their phosphorylation levels (a, b). In contrast, some of the mutant keratins contain four (K8) or five (K18) isoforms due to coexpression of the wild-type and mutant keratin with subsequent generation of altered charged species that have a slightly different mutation-induced isoelectric focusing point (d, f, g, h). (B): K8/K18 immunoprecipitates were prepared from normal liver or liver with the K18 T102A mutation, then analyzed by SDS-PAGE. The K18 bands were cut out, digested with trypsin, then analyzed with a MALDI-TOF mass spectrometer. Note that a peak position at 818.3 was detected only in the liver specimen with the K18 T102A mutation but not in normal liver. The mass difference of 30, between the wild-type and T102A K18 tryptic peptides (848.3 versus 818.3), corresponds to the HO-C-H species (two hydrogen, one oxygen and one carbon atoms with a mass of 30 daltons) that are present in threonine (the wild-type residue) but not in alanine (the mutant residue).

[008] ~~Fig. 3~~ Figures 3A-3C: K8 R340H mutation-proximal comparison of type II keratin sequences and confirmation of K8 R340H mutant protein expression in explanted livers. (A) Single letter abbreviations are used to represent amino acids. Bold dots represent amino acids that are identical to the K8 sequence. The shaded area highlights the conserved R340 of K8 and shows the histidine mutation we identified. Note that the K8 R340-containing motif (AEQ***R***GE) is highly conserved in type II keratins. It

is also conserved across species, being found in mouse and frog K8. (B) BHK cells were transiently cotransfected with K8/K18 WT or K8 R340H/K18 WT. K8/K18 immunoprecipitates were obtained from 1% NP40-solubilized cell lysates. The immunoprecipitates were analyzed by SDS-PAGE, followed by immunoblotting with anti-K8 R340 or anti-K8 H340 epitope-specific antibodies that preferentially recognized K8 WT or K8 R340H mutant, respectively. (C) K8/K18 immunoprecipitates were obtained from 1% NP40-solubilized normal liver or livers with the K8 R340H mutation. Samples were analyzed as described in panel B. Note that anti-K8 R340 (WT) recognizes K8 in the control patient (with K8 WT) and the patient with K8 R340H (lanes 1-6), whereas anti-K8 H340 (mutant) recognizes only patient livers with the K8 R340H mutation (lanes 2-6) but not the normal liver (lane 1). This indicates that the patients with K8 R340H mutation are heterozygous with regard to the keratin mutation. Arrowheads correspond to degraded K8.

[009] ~~Fig. 4~~ Figures 4A-4B: Keratin filament organization in human liver explants, and histologic findings of livers harboring the keratin mutations. (A): Human livers were sectioned, fixed in acetone and double-stained with rabbit anti-K8/18 or mouse anti-vimentin antibodies. Inset in panel i shows control double staining using fluorochrome-conjugated goat anti-rabbit and goat anti-mouse antibodies without adding any primary antibodies. All images were obtained using the same magnification. Bar in panel a = 20 μm. (B): Hematoxylin and eosin staining of explanted liver from two patients with acute fulminant hepatitis. Panel "a" is from a patient without a keratin mutation while panel "b" is from a patient with the K18 T102A mutation. The region outlined by a box in "b" is magnified in panel "c" to illustrate the cytoplasmic filamentous deposits noted primarily in livers of patients with keratin mutations.